

**Amendment to the Claims:**

This listing of claims will replace all prior versions, and listings, of the claims in the application.

**Listing of Claims:**

Claim 1 (withdrawn): A method for delivery of a therapeutic or diagnostic agent, the method comprising:

administering a fluid comprising a therapeutic or diagnostic agent to a preselected region within an organ, by forming a substantially closed chamber within or adjacent the organ, and delivering the fluid at a preselected pressure, flow rate or volume of administration to direct delivery of the fluid to the preselected region wherein the therapeutic or diagnostic agent is administered via the device of claim 61.

Claim 2 (withdrawn): The method of claim 1, wherein the preselected region is a histological layer of the organ.

Claim 3 (withdrawn): The method of claim 2, wherein the histological layer is selected from the group consisting of (a) an epithelial or subepithelial layer; (b) an endothelial or subendothelial layer; (c) a serosa or subserosal layer; and (d) an adventitial or subadventitial layer.

Claim 4 (withdrawn): The method of claim 1, wherein the organ comprises a blood vessel or a hollow viscus, and an interior volume of the blood vessel or hollow viscus is isolated to control the predetermined pressure, flow rate or volume of administration.

Claim 5 (withdrawn): The method of claim 1, wherein an external area of the organ is isolated to control the preselected pressure, flow rate, or volume of administration.

Claim 6 (withdrawn): The method of claim 1 further comprising:

forming a closed chamber within the organ by forming a closed chamber within a hollow organ space within the organ or forming a closed chamber around the organ or a portion of the organ; and

administering the fluid into the hollow organ space or the chamber around the organ; and

controlling at least one of a pressure, a flow rate, and a volume of the administration of the fluid in the closed chamber such that the agent is selectively delivered either to a region deep to a superficial layer, or substantially only to a superficial layer surrounding the hollow organ space, or is selectively delivered to the external surface of the organ, or substantially only to a layer deep to the external surface of the organ.

Claim 7 (withdrawn): The method of claim 1 wherein controlling at least one of the pressure, the flow rate, and the volume comprises determining a threshold pressure for disruption of microanatomic barriers that inhibit subepithelial delivery of the agent, and (a) administering the fluid at a pressure below the threshold pressure when delivery only to the superficial layer is desired, or (b) administering the fluid at a pressure at or above the threshold pressure when delivery to the region deep to the superficial layer is desired.

Claim 8 (withdrawn): The method of claim 1, wherein controlling at least one of the pressure, the flow rate, and the volume comprises controlling a liquid pressure.

Claim 9 (withdrawn): The method of claim 8, wherein controlling the liquid pressure comprises controlling a pressure gradient within or across the organ.

Claim 10 (withdrawn): The method of claim 8, wherein controlling the liquid pressure comprises administering the liquid at a constant pressure.

Claim 11 (withdrawn): The method of claim 1, wherein forming a closed chamber within a hollow organ space comprises accessing the hollow organ space, substantially occluding an outlet therefrom, and draining the hollow organ space to remove bodily fluids that may interfere with the action of the therapeutic or diagnostic agent.

Claim 12 (withdrawn): The method of claim 11 further comprising, after draining the hollow organ space, rinsing the hollow organ space so as to remove traces of bodily fluids that may interfere with the action of the therapeutic or diagnostic agent.

Claim 13 (withdrawn): The method of claim 6, further comprising, after administering the fluid comprising the therapeutic or diagnostic agent, draining the hollow organ space to remove the agent.

Claim 14 (withdrawn): The method of claim 13, further comprising, after draining the hollow organ space to remove the therapeutic or diagnostic agent, rinsing the hollow organ space to remove traces of the agent.

Claim 15 (withdrawn): The method of claim 6 wherein the superficial layer consists of epithelial cells surrounding the hollow organ space and the area deep to the superficial layer consists of areas deep to said epithelial cells.

Claim 16 (withdrawn): The method of claim 1 wherein controlling at least one of the pressure, the flow rate, and the volume comprises substantially occluding an outlet from a hollow organ space, and varying the flow rate or volume so as to obtain a desired pressure.

Claim 17 (withdrawn): The method of claim 1 wherein controlling at least one of the pressure, the flow rate, and the volume comprising administering a specified volume in a closed chamber.

Claim 18 (withdrawn): The method of claim 1, further comprising predetermining a threshold pressure, flow rate or volume for delivery to a selected anatomic or microanatomic site, and controlling at least one of a pressure, flow rate or volume to direct delivery of the agent to the selected site.

Claim 19 (withdrawn): The method of claim 18 wherein predetermining a threshold further comprises administering a test fluid into the closed chamber at a given flow rate and measuring a peak pressure at which delivery to a region deep to the superficial layer commences, and wherein controlling at least one of the pressure, the flow rate or the volume comprises administering the fluid (1) as part of a fluid flow into the closed chamber during which the peak pressure is not exceeded, when selective delivery only to a superficial layer is desired, or (2) as part of a fluid flow into the closed chamber during which the peak pressure is equaled or exceeded, when selective delivery to a region deep to the superficial layer is desired.

Claim 20 (withdrawn): The method of claim 1 further comprising administering a test fluid into the hollow organ space multiple times, at a given flow rate, and measuring respective multiple peak pressures at which delivery to a region deep to the superficial layer commences, and wherein controlling at least one of the pressure, the flow rate, and the volume comprises administering the fluid comprising the therapeutic or diagnostic agent (1) as part of a fluid flow during which the last-measured peak is not exceeded, when selective delivery only to a superficial layer is desired, or (2) as part of a fluid flow during which the last-measured peak pressure is equaled or exceeded, when selective delivery to a region deep to the superficial layer is desired.

Claim 21 (withdrawn): The method of claim 1 wherein the closed chamber comprises a hollow organ space, and controlling at least one of the pressure, the flow rate, and the volume comprises administering the fluid comprising the therapeutic or diagnostic agent at a pressure only slightly above a normal physiologic intraluminal pressure in the hollow organ space, at a pressure sufficient to achieve selective delivery substantially only to the superficial layer.

Claim 22 (withdrawn): The method of claim 21 wherein the fluid administered slightly above a normal physiologic intraluminal pressure is administered at a pressure no more than about 2-5 mg Hg above the normal physiologic intraluminal pressure in the hollow organ space.

Claim 23 (withdrawn): The method of claim 6 wherein the hollow organ space comprises a non-vascular interior of a hollow viscus.

Claim 24 (withdrawn): The method of claim 6 wherein the hollow organ space comprises the lumen of a duct.

Claim 25 (withdrawn): The method of claim 1 wherein the closed chamber comprises a hollow organ space, and the method further comprises isolating a portion of the hollow organ space within the body to form the substantially closed chamber.

Claim 26 (withdrawn): The method of claim 25 wherein isolating the portion of the hollow organ space comprises occluding a duct draining the organ.

Claim 27 (withdrawn): The method of claim 26 wherein the isolated portion of the hollow organ space comprises the hepatobiliary tract.

Claim 28 (withdrawn): The method of claim 25 wherein the isolated portion of the hollow organ space comprises the gall bladder and/or ducts of the hepatobiliary tract.

Claim 29 (withdrawn): The method of claim 25 wherein the isolated portion of the hollow organ space comprises hepatic bile ducts or at least a portion of intestine.

Claim 30 (withdrawn): The method of claim 7 wherein controlling at least one of the pressure, the flow rate and the volume comprises administering the fluid above the threshold pressure to the region deep to the superficial layer.

Claim 31 (withdrawn): The method of claim 20 wherein the fluid is administered above the threshold pressure, at a sufficient pressure to drive the therapeutic or diagnostic agent into a parenchyma of the organ.

Claim 32 (withdrawn): The method of claim 25 wherein the pressure drives the therapeutic or diagnostic agent into the parenchyma of the liver.

Claim 33 (withdrawn): The method of claim 1 wherein the therapeutic or diagnostic agent comprises at least one of a chemotherapy agent, a pro-inflammatory agent, an anti-inflammatory agent, and a genetic vector.

Claim 34 (withdrawn): The method of claim 6 wherein the therapeutic or diagnostic agent comprises a genetic vector, and at least one of a pressure, a flow rate, and a volume of the administration of the fluid is controlled such that selective delivery of the genetic vector is made substantially only to superficial cells adjoining the hollow organ space.

Claim 35 (withdrawn): The method of claim 6 wherein the hollow organ space comprises at least a portion of the hepatobiliary tract, the therapeutic or diagnostic agent comprises a genetic vector, and at least one of a pressure, a flow rate, and a volume of the administration of the fluid is controlled such that selective delivery is made to hepatocytes near the hollow organ space.

Claim 36 (withdrawn): The method of claim 6 wherein the hollow organ space is in an organ that includes a neoplasm, and the agent comprises an anti-neoplastic agent or a pro-inflammatory cytokine.

Claim 37 (withdrawn): The method of claim 6 wherein the hollow organ space comprises:

(a) a portion of the hepatobiliary system adjacent to or involved with hepatic fibrosis, primary biliary cirrhosis or sclerosing cholangitis, and the therapeutic or diagnostic agent comprises an anti-inflammatory agent; or

(b) a portion of intestine affected with Crohn's disease, and the therapeutic or diagnostic agent comprises an anti-inflammatory agent for delivery at a sufficient pressure to introduce the therapeutic or diagnostic agent to a subepithelial lamina propria of the intestinal wall; or

(c) a portion of hepatobiliary tract, the superficial layer comprises epithelial cells lining the hepatobiliary tract, and the region deep to the superficial layer comprises at least one of sinusoids of the liver, Space of Disse, lamina propria, and smooth muscle cells of the gall bladder; or

(d) a portion of the pancreas affected by pancreatic adenocarcinoma and the therapeutic agent comprises an anti-neoplastic agent or a pro-inflammatory agent or an agent that promotes the formation of blood vessels; and the agent is delivered to either the epithelial cells or subepithelial cells or both; or

(e) a portion of the esophagus affected by esophageal carcinoma and the therapeutic agent comprises an anti-neoplastic agent or a pro-inflammatory agent; or

(f) a portion of the prostate gland affected by prostatic carcinoma and the therapeutic agent comprises an anti-neoplastic agent or a pro-inflammatory agent; or

(g) a portion of the urinary bladder affected by carcinoma and the therapeutic agent comprises an anti-neoplastic agent or a pro-inflammatory agent delivered to either the superficial epithelial cells, the lamina propria, any or all of the circular and longitudinal muscle layers, and/or the serosa.

Claim 38 (withdrawn): The method of claim 1, wherein the agent comprises spherical particles having a diameter of no more than about 500 nm.

Claim 39 (withdrawn): The method of claim 1, wherein the agent is a nonparticulate agent.

Claim 40 (withdrawn): The method of claim 1, wherein the fluid is administered at a flow rate of 0.066-960  $\mu\text{l/sec}$ .

Claim 41 (withdrawn): The method of claim 1, wherein the fluid is administered at a flow rate of less than 1000  $\mu\text{l/sec}$ .

Claim 42 (withdrawn): The method of claim 41, wherein the fluid is administered at a pressure of no more than about 500 mm Hg.

Claim 43 (withdrawn): The method of claim 42, wherein the fluid is administered at substantially constant pressure.



Claim 44 (withdrawn): The method of claim 43, wherein the organ is non-vascular, and the fluid is administered at a substantially constant pressure of about 5-100 mm Hg.

Claim 45 (withdrawn): The method of claim 43, wherein the organ is vascular, and the fluid is administered at a substantially constant pressure of about 5-400 mm Hg.

Claim 46 (withdrawn): The method of claim 1, wherein pressure is controlled, and the method further comprises substantially constant monitoring of the pressure during administration of the fluid.

Claim 47 (withdrawn): The method of claim 1, further comprising administering a pharmacological substance that improves opening of tight junctions.

Claim 48 (withdrawn): The method of claim 1, wherein the organ is a hollow viscus, and the method further comprises partially filling the hollow viscus with an inflatable space occupier before administering the fluid.

Claim 49 (withdrawn): The method of claim 1, wherein the pressure is controlled by creating a pressure gradient in a solid portion of the organ, wherein the pressure gradient is preselected to deliver the agent to the predetermined region.

Claim 50 (withdrawn): The method of claim 49, wherein the pressure gradient is highest inside the organ.

Claim 51 (withdrawn): The method of claim 49, wherein the pressure gradient is highest outside the organ.

Claims 52-56 (canceled)

Claim 57 (withdrawn – currently amended): A method of delivering a therapeutic or diagnostic substance, the method comprising:

introducing a ~~flexible catheter~~ the device of claim 61 into an organ lumen lined with polar epithelial cells; and

infusing a therapeutic or diagnostic substance through the ~~catheter~~ the device into the organ lumen under preselected, controlled pressure conditions at which the therapeutic or diagnostic substance is delivered substantially only to apical surfaces of the epithelial cells and substantially not to any subepithelial regions.

Claim 58 (withdrawn): The method of claim 57 wherein the organ lumen is an hepatic or biliary duct and the therapeutic or diagnostic substance is infused at a pressure sufficient to deliver the agent substantially only to cholangiocytes lining the hepatic or biliary duct.

Claim 59 (withdrawn): The method of claim 57, further comprising infusing the therapeutic or diagnostic substance into the organ lumen under pre-selected, controlled pressure conditions at which the therapeutic or diagnostic substance is delivered not only to apical surfaces of the epithelial cells but also to subepithelial regions including basal surfaces of the epithelial cells.

Claim 60 (withdrawn): The method of claim 59 wherein the body lumen is an hepatic or biliary duct, and the therapeutic or diagnostic substance is infused at a sufficient pressure to deliver the agent to cholangiocytes, hepatocytes, or both.

Claim 61 (currently amended): An access device for targeted delivery of therapeutic or diagnostic agents, the access device comprising:

an elongated cannula having a wall, proximal and distal ends, and a lumen configured to contain a sharp-tipped trochar for penetrating a wall of a desired body organ having a hollow space therein; ~~and~~

first and second balloons spaced axially along the cannula at positions such that, when the cannula is inserted through the wall of the desired body organ and the balloons are inflated, the first balloon engages an inner face of the organ and the second balloon engages an outer face of the organ, holding the distal end of the cannula in position within the hollow space inside the organ and substantially sealing against leaks; and

a flexible catheter having an exterior and a distal tip, the catheter being capable of insertion through the cannula, the catheter including an inflatable balloon near its distal tip, that upon inflation is capable of occluding a duct communicating with the desired body organ into which organ the cannula is introduced.

Claim 62 (original): The access device of claim 61 further comprising a drainage line communicating with a drainage inlet distal to the first and second balloons.

Claim 63 (original): The access device of claim 61 further comprising inflation ports positioned at or near the proximal end of the cannula for inflating the first and second balloons.

Claim 64 (original): The access device of claim 61 further comprising a selectively removable occluder that selectively closes the cannula.

Claim 65 (original): The access device of claim 64 wherein the occluder comprises a cannula cap.

Claim 66 (original): The access device of claim 61 wherein the cannula consists of bio-compatible materials.

Claim 67 (canceled)

Claim 68 (currently amended): The access device of claim ~~67~~ 61, wherein the catheter comprises multiple lumens, and one of the multiple lumens communicates with the exterior of the catheter proximally of the inflatable balloons.

Claim 69 (currently amended): The access device of claim ~~67~~ 61 wherein at least one of the multiple lumens communicates with the exterior of the catheter distally of the inflatable balloon.

Claims 70-78 (canceled)

Claim 79 (new): The access device of claim 61 further comprising a pressure transducer at or near the distal tip of the catheter.

Claim 80 (new): The access device of claim 61 wherein the catheter comprises multiple lumens, and at least one of the catheter lumens is configured for sensing pressure within the desired body organ.